## REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 3, 4, 16-28, 31, 32, 44-60 and 61-74 are in this case. Claims 3, 4, 16-28, 31, 32 and 44-60 have been withdrawn as being drawn to a non-elected invention. Claims 61-74 have been rejected. Claim 61 has now been amended.

### *Objections to Embedded Hyperlink*

The Examiner has again objected to the hyperlinks presented on page 15 and has suggested removal of all occurrences of "http://" from this page in order to overcome this objection. As instructed above, Applicant has now elected to remove all such occurrences from the specification thereby traversing the specification objections.

### *35 U.S.C. § 112, Second Paragraph*

The Examiner has rejected claims 61-74 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The Examiners rejections are respectfully traversed. Claim 61 has now been amended.

The Examiner has stated that the phrase "selectively hybridizes" in claim 61 is not clearly defined in the specification. In the interest of expediting prosecution of this case, Applicant has elected to amend claim 61 to now recite "each oligonucleotide of said plurality of oligonucleotides hybridizes to a set of RNA splice

variants produced from only one transcription unit". This feature of the oligonucleotides of the present invention is clearly supported by the instant specification, see for Example, Figure 3 of the filed application.

***35 U.S.C. § 102 (e) Rejection - Schweighoffer et al.***

The Examiner has rejected claims 61-74 under 35 U.S.C. § 102(e) as being anticipated by Schweighoffer et al. (US 6,251,590 B1). The Examiner's rejections are respectfully traversed. Claim 61 has now been amended.

The Examiner states that Schweighoffer et al. teach an oligonucleotide library comprising a plurality of oligonucleotides capable of hybridizing to alternative forms of splicing mRNAs typical of a pathological condition.

The Examiner further states that as is evident from the text on column 9, lines 36-41, Schweighoffer et al. teach of a screening library which includes a whole set of spliced variants, thereby anticipating the claimed splice variant set of the present invention.

Contrary to the Examiner's assertion, Schweighoffer et al. do not teach or suggest the transcript set of the present invention. The transcript set referred to by Schweighoffer et al. is a set of transcripts resultant from subtractive hybridization between mRNAs (or cDNAs) representative of normal and pathological tissues. As such this "set" of transcripts is a set of mRNAs which includes splice variants unique to a pathology (i.e., present in a library representing pathological tissue and absent from normal tissue or another pathological tissue). Such a set typically includes a collection of unique transcripts, transcribed under specific pathological conditions,

and as such does not include several splice variants of a single gene (transcription unit). In fact, it is these unique transcripts which interest Schweighoffer et al., since they constitute markers for qualitative analysis of tissues, i.e., determination of presence or absence of a pathology. Thus, obtaining unique splice variants characteristic of a pathological tissue (or any other specific tissue) and generating oligonucleotide probes specific to such unique splice variants is the only goal of this reference. Indeed, as is clearly illustrated by the following text excerpts, this goal is repeated throughout US 6,251,590 (emphasis added in text excerpts below) indicating that this reference neither anticipates nor renders obvious, but rather teaches away from, the present invention.

> The instant invention describes a set of original methods aimed at identifying differences in splicing occurring between two distinct pathophysiological conditions. Identifying such differences provides information on qualitative but not on quantitative differences as has been the case for techniques described so far. The techniques disclosed in the present invention are hence all encompassed under the term of "qualitative differential screening"(Column 1, lines 38-44)

> This or these cross hybridization procedures allow one to demonstrate in a convenient manner unpaired regions, i.e. regions present in RNAs in one physiological condition and not in RNAs from another physiological condition. Such regions essentially correspond to alternative forms of splicing, typical of a given physiological state, and thus form genetic elements or markers of particular use in the fields of therapeutics and diagnostics as set forth below.(Column 2, lines 26-33)

> As indicated above, the qualitative differential screening according to the invention allows the identification of

> nucleic acids characteristic of a particular physiological condition (condition B) in relation to a standard (reference) physiological condition (condition A), that are to be cloned or used for other applications. (Column 3, lines 16-21)

> The different methods disclosed hereinabove thus all lead to the cloning of cDNA sequences representative of differentially spliced genetic information between two pathophysiological conditions. The whole set of clones derived from these methods makes it thus possible to construct a library representative of qualitative differences occurring between two conditions of interest.(Column 8, line 63 - Column 9, line 2)

> The present application is further directed to any nucleic acid library comprising nucleic acids specific of alternative forms of splicing typical of a physiological condition. These libraries conveniently comprise cDNAs, generally of double stranded nature, corresponding to RNA regions specific of alternative splicing.(Column 10, lines 12-17)

> One of the major strengths of these techniques is, indeed, the identification, within a messenger, and consequently within the corresponding protein, of the functional domains which are affected in a particular disorder. This makes it possible to assess the importance of a given domain in the development and persistence of a pathological state.(Column 12, lines 42-47)

In sharp contrast, the set of mRNA transcripts described and claimed by the present invention is a set transcribed from a single transcription unit (i.e., gene). Such a set represents the alternatively spliced mRNA forms produced from a single gene.

Identifying such a set and determining the sequence region shared by transcripts of this set enables generation of oligonucleotides which are particularly

useful for quantitative hybridization, since an oligonucleotide which is capable of specifically hybridizing with a sequence region shared by transcripts of such a set enables detection of the transcript set produced from a single gene, thus providing more accurate information as to the expression level of this gene. Such quantitative analysis is not possible with the oligonucleotides of Schweighoffer et al. since they are designed to be specifically hybridizable with only one transcript of a gene ("these libraries conveniently comprise cDNAs, generally of double stranded nature, corresponding to RNA regions specific of alternative splicing" Column 10, lines 12-17), since this transcript is a marker for a condition.

In order to further illustrate these fundamental differences between Schweighoffer et al. and the present invention, Applicant has enclosed herewith a diagram which clearly demonstrates the differences (both in sequence and function) between an oligonucleotide of the library of the present invention and an oligonucleotide proposed by Schweighoffer et al.

As is shown by the diagram, an oligonucleotide of the library of the present invention (top half of the diagram) is designed specific to a region (marked as B) shared by a set of transcripts which are produced from a single transcription unit (gene), whereas in Schweighoffer et al., (bottom half of the diagram) a library oligonucleotide is designed so as to specifically hybridize with a sequence region (A) which is unique to a single transcript (i.e., not shared by the transcripts), since it is this unique transcript which is expressed under a specific condition (e.g., pathology) and thus it represents a putative marker for the specific condition.

It is therefore the Applicant's strong opinion that Schweighoffer et al. do not anticipate nor render obvious the present invention as claimed.

In view of the above arguments, Applicant believes that the 35 U.S.C. § 102(e) rejections have been overcome.

In view of the above amendments and remarks it is respectfully submitted that claims 61-74 are now in condition for allowance. Prompt Notice of Allowance is respectfully and earnestly solicited.

Respectfully submitted,

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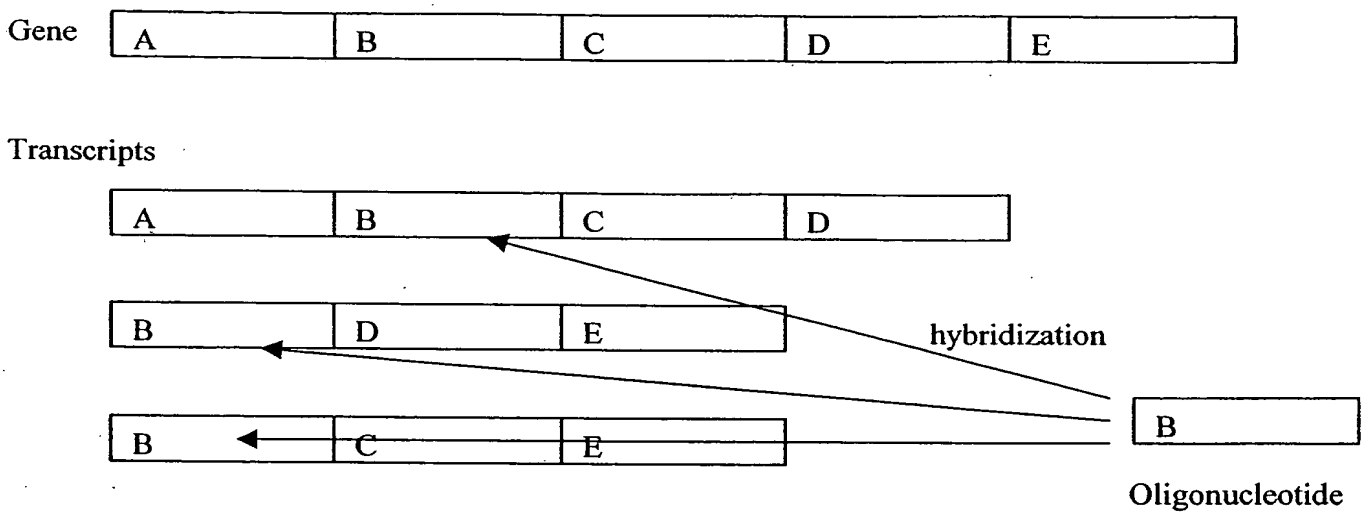
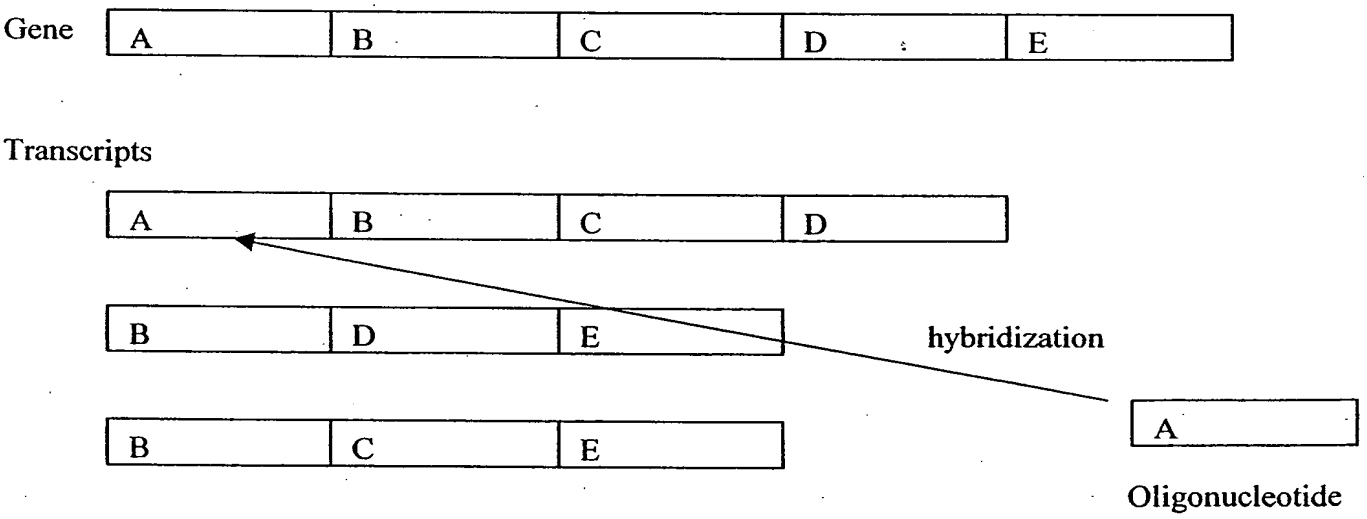
***Encl.***
Petition for three-month extension fee
Diagram

Present Invention QUANTIFICATION




Total amount of mRNA transcribed from a specific gene

Schweighoffer QUALIFICATION




Absence or presence of a specific transcript in a sample